The presently claimed invention is also directed to a method of treating a corneal epithelial disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound having an effect of activating Rho.

Claims 1 to 7 were rejected under 35 USC 102 as being anticipated by Liliom et al., Am Phys. Soc., 274, C1065-C1074 (1998).

Liliom et al. tested the effect of oleyl lysophosphatidic acid ("LPA") for promoting proliferation for only corneal keratocytes. The present claims, however, relate to a therapeutic agent composition for a corneal epithelial disorder and to a method for treating a corneal epithelial disease. The present invention does not relate to corneal disorders of keratocytes.

Thus all of the disorders recited in applicants' claims 4 to 7 of corneal ulcer, corneal erosion, keratitis and dry eye are symptoms caused by corneal epithelial defects.

Although Liliom et al. tested the effect of oleyl lysophosphatidic acid ("LPA") for promoting proliferation for corneal keratocytes, Liliom et al. did not test for an effect of

LPA on corneal epithelial cells (see columns 1 and 17 of Liliom et al.). The presently claimed invention is novel, since Liliom et al. do not describe an effect of LPA for (i) promoting proliferation for corneal epithelial cells and (ii) therapeutic effects on corneal epithelial disorders.

The cornea consists mainly of an epithelial layer, a stromal layer and an endothelial layer. The thickness of the epithelial layer is about one tenth as thick as that of the cornea, whereas the thickness of the stromal layer is about nine tenths as thick as that of the cornea. The corneal epithelial layer protects the eyeball from external stimulation as a barrier to shut-off the corneal stromal layer from outside of the eyeball, whereas the corneal stromal layer participates in the maintenance of water in the cornea and greatly affects transparency of the cornea. The corneal epithelial layer has a five- to six-layer structure of corneal epithelial cells, and the cells are changed in a turnover of about one week. On the other hand, the corneal stromal layer has keratocytes, which are mesenchyme cells, scattered in the stromal layer consisting of an extracellular matrix, and it is said that a turnover of the keratocytes takes two to three years.

Accordingly, corneal epithelial cells are substantially different from keratocytes in structure, function, etc.

Attached to applicants' AMENDMENT UNDER 37 CFR 1.111 dated November 21, 2002 was a copy of Steven E. Wilson et al., Investigative Ophthalmology & Visual Science, July 1993, Vol. 34, No. 8, 2544-2561, which describes on pages 2554 and 2555 that EGF (epidermal growth factor) has effects for promoting the proliferation for all of epithelial cells, keratocytes and endothelial cells of the cornea (see Figs. 8 and 9 of Wilson et al.). On the other hand, it is shown that HGF (hepatocyte growth factor) and KGF (keratocyte growth factor) promote the proliferation of epithelial cells and endothelial cells, but does not promote the proliferation of keratocytes.

Since epithelial cells, keratocytes and endothelial cells of the cornea differ in structure and role, it is respectfully submitted that one of ordinary skill in the art could not have predicted whether or not the compounds having an effect of activating Rho of the present invention would have an effect for promoting the proliferation of the corneal epithelial cells, until pharmacological tests are carried out.

Withdrawal of the anticipation rejection in view of Liliom et al. is thus respectfully requested.

Claims 8 to 16 were rejected under 35 USC 102 as being anticipated by SunderRaj et al., Investigative Ophthalmology and Visual Science, 1998, Vol. 39, No. 7, pages 1266-1272 for the reasons set forth at the middle of page 2 of the Office Action.

Claims 17 and 18 were rejected under 35 USC 103 as being unpatentable over SunderRaj et al. for the reasons set forth in the paragraph bridging pages 2 and 3 of the Office Action.

It was admitted in the Office Action that SunderRaj et al. differ from the claimed invention in the route of administration and the dosages used.

SundarRaj et al. disclose that Rho kinase ("ROCK-I") transits from the limbus to the cornea and is localized in the corneal epithelium. However, SundarRaj et al. did not test the pharmacological actions of ROCK-I on corneal epithelial disorders.

On page 1271, at the bottom of the right column, as a conclusion, SundarRaj et al. state that ROCK-I signaling pathways are likely to have important functions in corneal epithelial differentiation, maintenance, wound healing, and development,

which will be explored in future studies. Namely, SundarRaj et al. conclude that it is a future subject to clarify a relationship among ROCK-I, corneal epithelial differentiation and the like.

Thus, SundarRaj et al. disclose that ROCK-I transits from the limbus to the cornea and is localized in the corneal epithelium, but SundarRaj et al. did not test what kind of pharmacological action ROCK-I has on corneal epithelial disorders. The fact that ROCK-I transits from the limbus to the cornea and is localized in the corneal epithelium is at best only an invitation for future studies with respect to whether or not ROCK-I is likely to have any important functions in corneal epithelial differentiation, maintenance and wound healing. Accordingly, it is unclear from SundarRaj et al. if ROCK-I exhibits a positive or a negative action on the healing of corneal epithelial disorders, and such action could not be clarified until pharmacological tests have been carried out.

As discussed above, since SundarRaj et al. do not disclose what kind of action compounds having an effect of activating Rho exhibit with respect to corneal epithelial disorders, the present

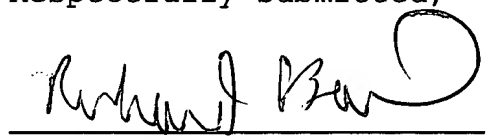
invention is not anticipated or rendered obvious by SundarRaj et al.

It is therefore respectfully submitted that applicants' claimed invention is not anticipated and is not rendered obvious by each of the references.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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